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FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

534/MAS/2002
17/07/02

Novel Crystalline Polymorphic forms of Dutasteride and Process for preparation thereof

Complete After Provisional
... 26 JUN 2003

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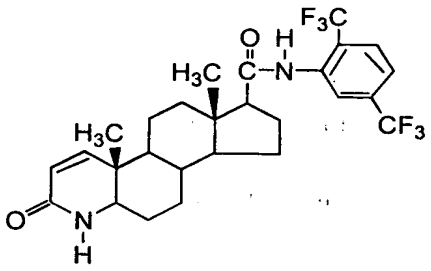
7-1-27, Ameerpet
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of the Invention:

The present invention relates to novel crystalline polymorphic forms of Dutasteride, which is chemically known as 17β-N-[2,5-bis (Trifluoromethyl)phenyl]carbamoyl-4-aza-5-α-androst-1-en-3-one and shown as Formula (I). The present invention also relates to process for preparing the novel crystalline polymorphic forms of Dutasteride. More specifically as per our provisional specification (application No: 534/MAS/2002) the present invention relates to the novel crystalline polymorphic form -II of Dutasteride and process for the preparation of crystalline form I & II of 17β-N-[2,5-bis (Trifluoromethyl)phenyl]carbamoyl-4-aza-5-α-androst-1-en-3-one (Dutasteride).



Formula (I)

Dutasteride is useful in the treatment of androgen responsive and mediated diseases.

Background of the invention:

US Patent 5,565,467 claimed Dutasteride and its related compounds. It also claimed the pharmaceutical formulations thereof and their use in the treatment of androgen and mediated diseases.

The '467 patent discloses a process for the preparation of Dutasteride, which comprises the dehydrogenation of 17β-N-(2,5-bis (Trifluoromethyl) phenyl) carbamoyl-4-aza-5α-

androstane-3-one in the presence of catalysts 2,3 -dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) and bis (tri methylsilyl) trifluoroacetamide in dioxane as solvent and the resultant solid is crystallized from a mixture of ethyl acetate - heptane in a ratio of 1:1 v/v.

WO 9507927 disclosed the process for isolation of pure Dutasteride by crystallization of crude Dutasterde in methanol and acetonitrile.

No relevant references of Dutasteride were disclosed the crystalline Polymorphic forms till date.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphs, polymorphic modification or form.

Hence, the first object of the present invention is to provide the novel crystalline forms of Dutasteride.

The second object of the present invention is the process for the preparation of the novel crystalline forms of Dutasteride. The crystalline forms of Dutasteride of present invention are designated as Form-I and Form-II for convenience.

The crystalline forms of the present invention are characterized by X-ray diffractogram pattern. The XRD patterns are well distinguished to each other indicating the difference in the crystalline structure.

The novel crystalline forms of Dutasteride may be well suited for pharmaceutical formulations and can be used in the treatment of androgen and mediated diseases.

Brief description of accompanying drawings:

Fig-1: X-Ray powder diffractogram of Dutasteride Form-I.

Fig -2: X-Ray powder diffractogram of Dutasteride Form-II.

Fig.-3: Infrared spectrum of Dutasteride Form-II

Summary of the invention:

The present invention provides novel crystalline forms of Dutasteride and process for preparation thereof. The novel crystalline forms of present invention are designated as Form-I and Form-II. The crystalline Form-I and Form-II of Dutasteride are characterized by X-ray diffractogram pattern. The process for the preparation of these crystalline forms comprises the dissolution of Dutasteride in polar organic solvents accompanied by distillation of the solvent and further isolation by adding an organic solvent, preferably less polar than initial solvent to afford the novel crystalline forms.

Detailed description of the invention:

The present invention provides the novel crystalline Form-I and Form-II of Dutasteride and process for their preparation.

The crystalline Form-I and Form-II of Dutasteride of present invention is characterized by X-ray diffractogram, which are measured on Bruker Axe, DS Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The process for the preparation of novel crystalline Form-I of Dutasteride comprises:

(i) dissolving the crude Dutasteride in halogenated hydrocarbon solvents, preferably dichloromethane;.

(ii) distilling the solvent from the reaction solution;

(iii) adding the low molecular aliphatic hydrocarbon solvent such as cyclohexane to the resultant residue obtained in step (ii);

(iv) filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-I of Dutasteride.

The crystalline Form-I of Dutasteride obtained in the above process is characterized by the X-ray powder diffraction pattern. The d-spacings (in ^{O}A) of the identified peaks in the X-ray diffractogram are 16.85,8.59, 7.44, 6.93, 6.29,5.95, 5.63, 5.58, 5.32, 4.98, 4.89, 4.78, 4.49, 4.32, 4.10, 4.04, 3.86, 3.75,3.59, 3.46, 3.30, 3.17, 2.95, 2.75, 2.65, 2.39 and 2.23.

The process for the preparation of novel crystalline Form-II of Dutasteride comprises:

(i) dissolving the crude Dutasteride in alcoholic solvents having C_1-C_5 carbon atoms, preferably methanol;.

(ii) distilling the solvent from the reaction solution;

(iii) adding ester solvents such as ethyl acetates to the resultant residue obtained in step (ii);

(iv) filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-II of Dutasteride.

The crystalline Form-II of Dutasteride obtained in the above process is characterized by the X-ray powder diffraction pattern. The d-spacings (in ^{O}A) of the identified peaks in the X-ray diffractogram are 13.42, 12.25, 10.18, 9.43, 8.64, 8.34, 7.98, 7.41, 6.96, 6.80, 6.13, 5.93, 5.84, 5.27,5.12, 4.93, 4.77, 4.70, 4.58, 4.46, 4.29, 4.08, 3.99, 3.91, 3.82, 3.63, 3.45, 3.29, 3.18, 3.12, 2.94, 2.35, and 2.30.

Hence, the present invention is directed to provide novel crystalline forms of Dutasteride and process for the preparation thereof. The process for the preparation of crystalline forms of Dutasteride of the present invention is simple, eco-friendly and commercially viable.

The process of the present invention will be explained in more detail with reference to the following examples, which are provided by way of illustration only and should not be constructed as limit to the scope of the reaction in any manner.

Example-1:

Process for the preparation of crystalline Form-I of Dutasteride.

Dissolved 5.0grams of crude Dutasteride (prepared as per the prior art methods) in 25 ml of dichloromethane under stirring. Distilled off the solvent partially(about 80 %) under reduced pressure. To the resulted residue added 50ml of cyclohexane and stirred at 50-60°C for about 45minutes. Filtered the separated solid at 50-60°C followed by washed with 10ml of cyclohexane. Dried the obtained solid at 80-90°C for 3 hours to get the desired crystalline Form-I of Dutasteride (4.5 grams, 90% of yield).

Example-2:

Process for the preparation of crystalline Form-II of Dutasteride.

Charged 30.0grams of crude Dutasteride (prepared as per the prior art methods) and 210ml of methanol into one liter round bottomed flask. Heated to reflux for complete dissolution and to get clear solution. Charged 3grams of charcoal to the reaction mass and stirred at the same temperature for 15 minutes. Filtered the contents through hyflow bed and washed with 30ml of methanol. Concentrated the filtrate under reduced pressure and charged 30ml of ethyl acetate followed by distillation off complete solvents under reduced pressure. Charged 90ml of ethyl acetate to the residue and stirred at 60-65°C. cooled the reaction solution to 25-35°C and stirred at the temperature for 45 minutes. Filtered the separated solid and washed with 30ml of ethyl acetate. Dried the obtained solid at 70-80°C up to get the constant weight of the desired crystalline Form-II of Dutasteride(22 grams, 73.3%of yield)

Claims

1. Novel crystalline Form-II of 17β-N-[2,5-bis (Trifluoromethyl)phenyl]carbamoyl-4-aza-5-α-androst-1-en-3-one (Dutasteride).
2. According to claim-1 the d-spacing (in °A) of X-ray powder diffraction pattern of novel crystalline Form-II of Dutasteride comprises of 13.42, 6.96, 6.13, 5.27,4.77, 4.70, 4.58, 4.46 and 3.82.
3. According to claim-2, the 2-theta values of X-ray powder diffraction of novel crystalline Form-II of Dutasteride comprises 6.580,12.712,14.445,16.796,18.575, 18.877,19.382,19.907 and 23.258.
4. According to claims 1,2 and 3 the X-ray powder diffraction of novel crystalline Form-II of Dutasteride as depicted in figure-1.
5. The infrared spectrum of novel crystalline Form-II of Dutasteride which comprises 818.56, 835.98, 1041.23,1087.77,1218.92,1238.97,1263.35,1317.75,1365.64,1434.43, 1593.48,1673.62,2873.06,2943.03,3197.02,3295.55, 3391.29 and 3449.55 cm-1.
6. The process for the preparation of novel crystalline Form-II of Dutasteride which comprises ,
   (i) dissolving the crude Dutasteride in alcoholic solvents having C_1-C_5 carbon atoms, preferably methanol;.
   (ii) distilling the solvent from the reaction solution;
   (iii) adding ester solvents such as ethyl acetates to the resultant residue obtained in step (ii);
   (iv) filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-II of Dutasteride.

7. The process for the preparation crystalline Form-I of Dutasteride which comprises,

(i) dissolving the crude Dutasteride in halogenated hydrocarbon solvents, preferably dichloromethane;.

(ii) distilling the solvent from the reaction solution;

(iii) adding the low molecular aliphatic hydrocarbon solvent such as cyclohexane to the resultant residue obtained in step (ii);

filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-I of Dutasteride.

8. Novel crystalline Form-II of 17β-N-[2,5-bis (Trifluoromethyl)phenyl]carbamoyl-4-aza-5-α-androst-1-en-3-one (Dutasteride),which is substantially as here in described and exemplified.

Dated: 14th day of June 2003.

Signed)_____

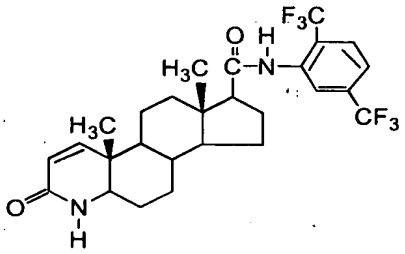
Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the invention: "Novel Crystalline Polymorphic forms of Dutasteride and Process for preparation thereof"

The present invention provides novel crystalline forms of Dutasteride and process for preparation thereof. The novel crystalline forms of present invention are designated as Form-I and Form-II. The crystalline Form-I and Form-II of Dutasteride are characterized by X-ray diffractogram pattern. The process for the preparation of these crystalline forms comprises the dissolution of Dutasteride in polar organic solvents accompanied by distillation of the solvent and further isolation by adding an organic solvent, preferably less polar than initial solvent to afford the novel crystalline forms.

Dutasteride can be depicted by the Formula (I).



Formula (I).

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Figure 1 of 3.

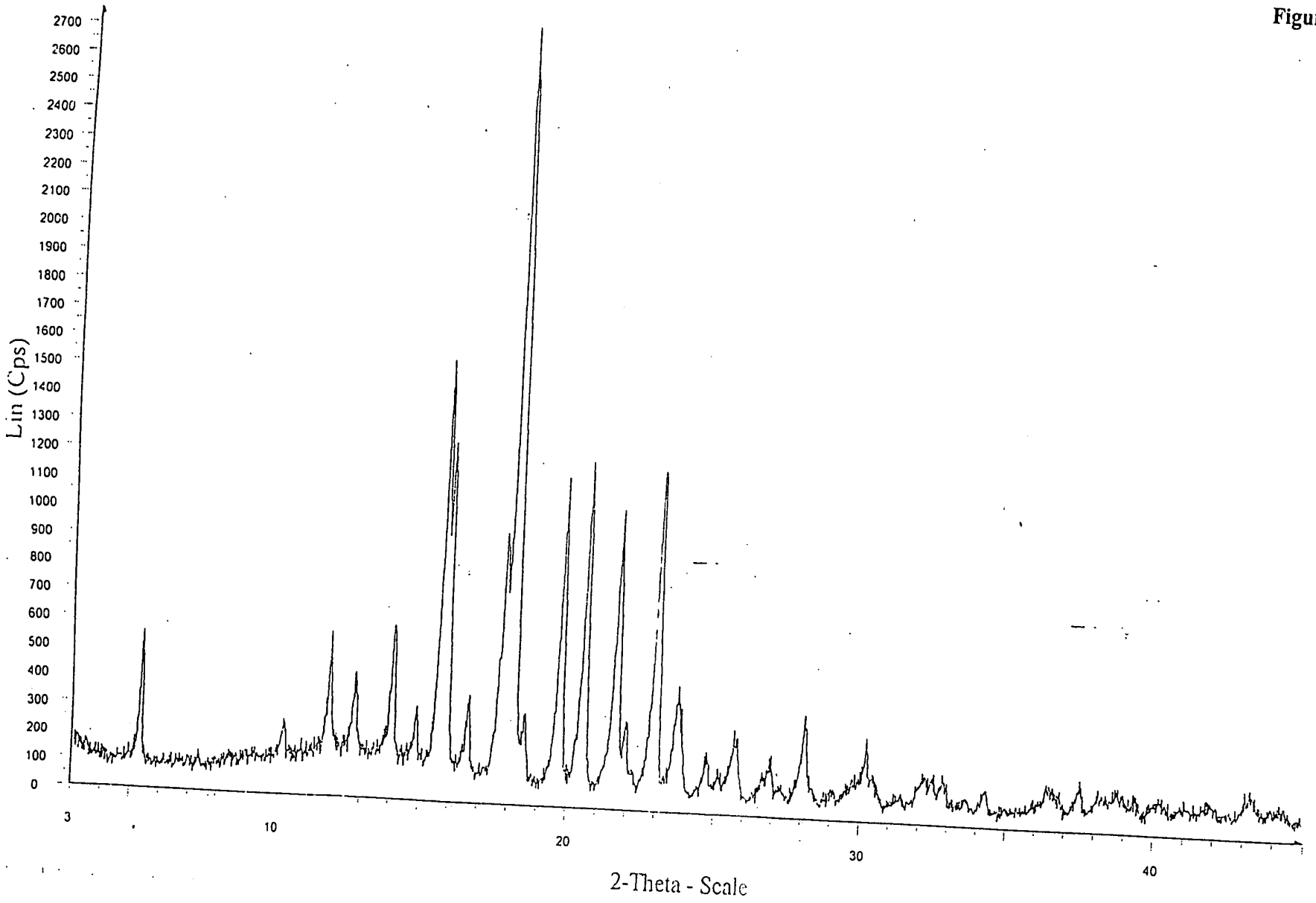

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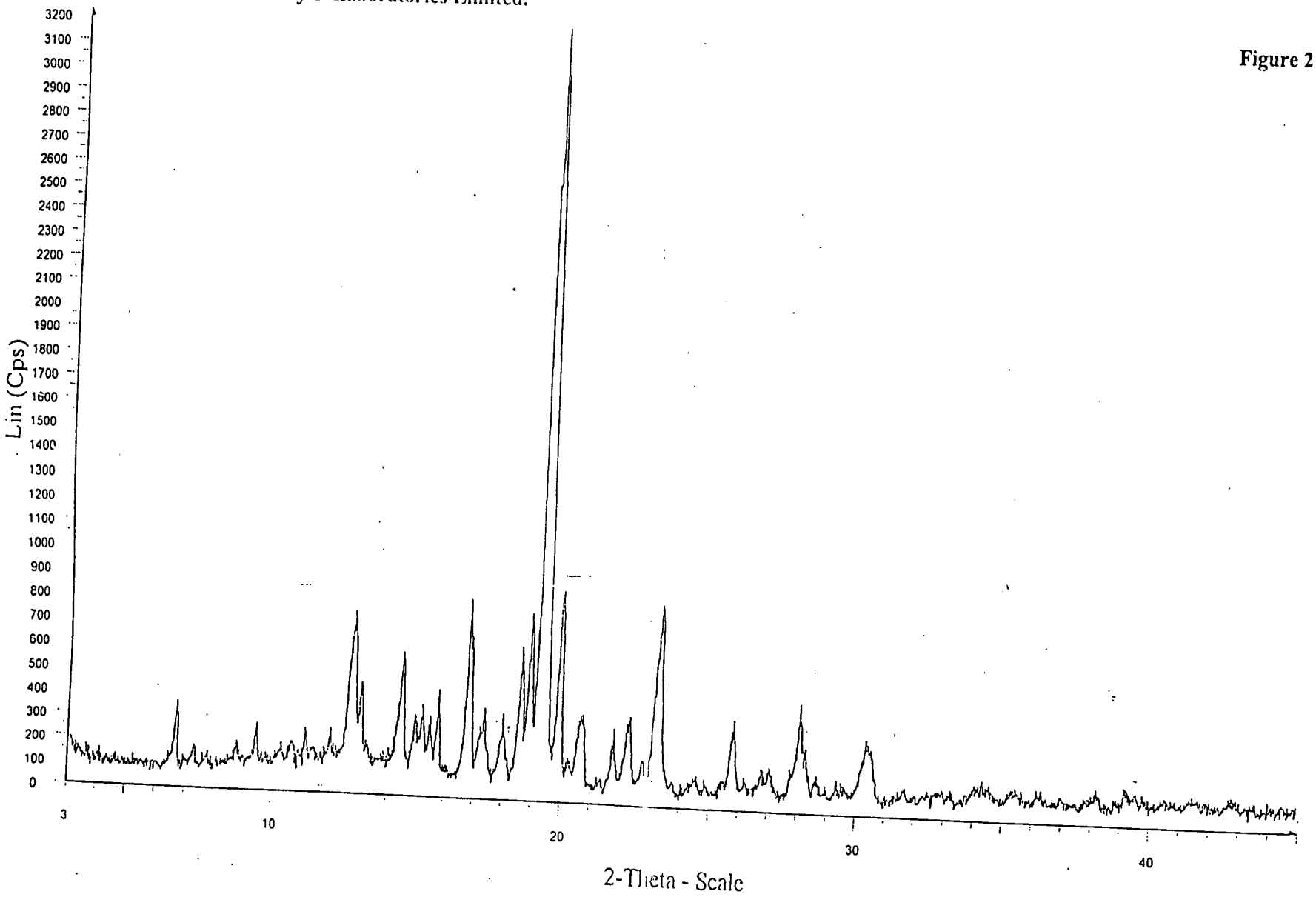
Figure 2 of 3.



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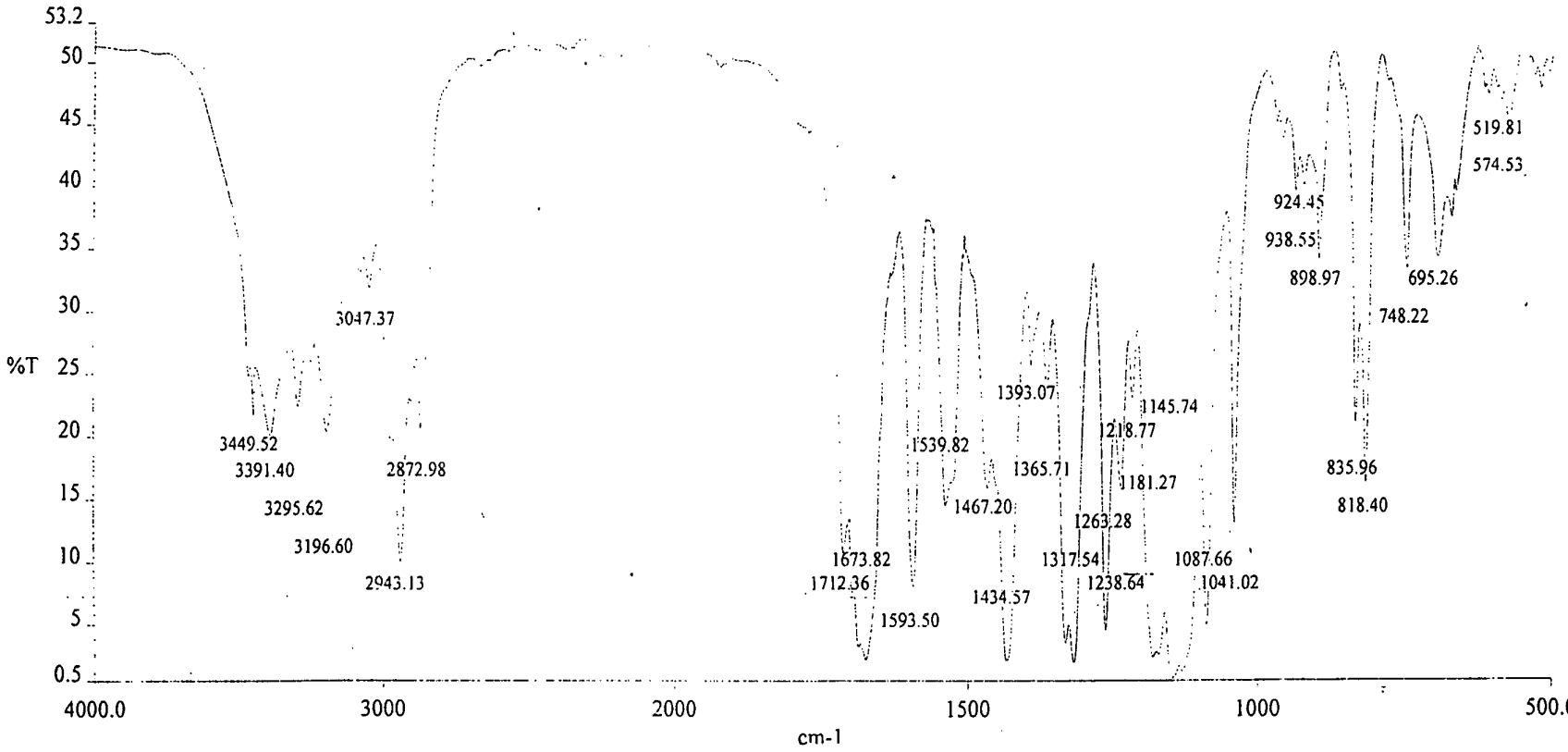

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